

Chromosome 11p15.5 Regional Imprinting: Comparative Analysis of KIP2 and H19 in Human Tissues and Wilms' Tumors

Wai-Yee Chung*, Luwa Yuan*, Lin Feng*, Terrence Hensle⁺
and Benjamin Tycko* (*Department of Pathology and
⁺Department of Surgery, College of Physicians and Surgeons,
Columbia University)

Genomic imprinting leads to parent-of-origin-dependent gene silencing with monoallelic RNA expression in tissues of the offspring. In the region of human chromosome 11p15.5, which is associated with the Beckwith-Wiedemann syndrome (BWS) and is subject to recurrent maternal loss of heterozygosity (LOH) in embryonal tumors such as Wilms' tumor (WT) and embryonal rhabdomyosarcoma (RMS), there are two well-studied imprinted genes: H19, which is paternally imprinted, and IGF2, which is silenced on the maternal allele. Recently, the human KIP2 gene, which encodes a cyclin-cdk inhibitor and which has been proposed as a candidate tumor suppressor gene, has been localized centromeric to IGF2 and close to the positions of several chromosomal translocation breakpoints in kindreds with BWS.

Recent observations have suggested the existence of chromosomal domains containing clusters of imprinted genes which could have important implications both for the mechanism of imprinting and for the mode of disregulation of imprinted genes in human diseases. To test the possibility of coordinate disruption of imprinting of multiple 11p15.5 genes in these tumors, we have characterized total and allele-specific mRNA expression levels via Northern analysis and DNA methylation by Southern blotting of the 11p15.5 KIP2 gene in normal human tissues, WTs and RMS.

Both KIP2 alleles are expressed, but there is a bias with the maternal allele contributing 70-90% of mRNA which suggests the presence of one or more paternally imprinted tumor suppression genes in this chromosomal region. Tumors with LOH show moderate to marked reductions in KIP2 mRNA relative to control tissues, and residual mRNA expression is from the imprinted paternal allele. Among WTs without LOH, most cases with H19 inactivation also have reduced KIP2

expression and most cases with persistent H19 expression have high levels of KIP2 mRNA. In contrast to the extensive hypermethylation of the imprinted H19 allele, both KIP2 alleles are hypomethylated and WTs with biallelic H19 hypermethylation lack comparable hypermethylation of KIP2 DNA. 5-aza-2'-deoxycytidine (aza-C), a demethylating drug which has been widely used as a probe for the methylation-dependence of expression of imprinted genes, increases H19 expression in RD RMS cells but does not activate KIP2 expression.

These data indicate coordinately reduced expression of two linked paternally imprinted genes in most WTs and also suggest mechanistic differences in the maintenance of imprinting at these two loci. In conclusion, it appears that WTs formation is increasingly likely to be promoted by the aberrant expression of multiple imprinted genes in an extended domain of chromosome 11p15.5 with a bipaternal epigenotype not only in the cases with LOH, but also in about half of the cases which retain heterozygosity. (*Human Molecular Genetics, 1996, vol5, No 8*)

[HOME](#) [HELP](#) [FEEDBACK](#) [SUBSCRIPTIONS](#) [ARCHIVE](#) [SEARCH](#) [TABLE OF CONTENTS](#)

QUICK SEARCH:	
Author:	Keywor
<input type="text"/>	<input type="text"/>
<input type="button" value="Go"/>	
Year:	Vol:

Institution: PC43PT0608040 [Sign In as Member / Individual](#)

Proceedings of the National Academy of Sciences, Vol 91, 5513-5517,
Copyright © 1994 by National Academy of Sciences

ARTICLE

Three Tumor-Suppressor Regions on Chromosome 11p Identified by High-Resolution Deletion Mapping in Human Non-Small-Cell Lung Cancer

G Bepler and MA Garcia-Blanco

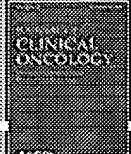
Non-small-cell lung cancer is the leading cause of cancer death for men and women in the industrialized nations. Identification of regions for genes involved in its pathogenesis has been difficult. Data presented here show three distinct regions identified on chromosome 11p. Two regions on 11p13 distal to the Wilms tumor gene WT1 and on 11p15.5 between the markers HBB and D11S860 are described. The third region on the telomere of 11p15.5 has been previously described and is further delineated in this communication. By high-resolution mapping the size of each of these regions was estimated to be 2-3 megabases. The frequency of somatic loss of genetic information in these regions (57%, 71%, and 45%, respectively) was comparable to that seen in heritable tumors such as Wilms tumor (55%) and retinoblastoma (70%) and suggests their involvement in pathogenesis of non-small-cell lung cancer. Gene dosage analyses revealed duplication of the remaining allele in the majority of cases in the 11p13 and the proximal 11p15.5 region but rarely in the distal 11p15.5 region. In tumors with loss of heterozygosity in all three regions any combination of duplication or simple deletion was observed, suggesting that loss of heterozygosity occurs independently and perhaps at different points in time. These results provide a basis for studies directed at cloning potential tumor-suppressor genes in these regions and for assessing their biological and clinical significance in non-small-cell lung cancer.

- [Reprint \(PDF\) Version of this Article](#)
- Similar articles found in:
 - [PNAS Online](#)
 - [PubMed](#)
 - [PubMed Citation](#)
- This Article has been cited by:
 - [other online articles](#)
- Search PubMed for articles by:
 - [Bepler, G. || Garcia-Blanco, M. A.](#)
- Alert me when:
 - [new articles cite this article](#)
- [Download to Citation Manager](#)

This article has been cited by other articles:

 THE ANNALS OF THORACIC SURGERY [► HOME](#)

E. B. Lee, T. I. Park, S. H. Park, and J. Y. Park
Loss of heterozygosity on the long arm of chromosome 21 in non-small cell lung cancer
Ann. Thorac. Surg., May 1, 2003; 75(5): 1597 - 1600.
[Abstract] [Full Text] [PDF]

 JOURNAL OF CLINICAL ONCOLOGY [► HOME](#)

G. Bepler, A. Gautam, L. M. McIntyre, A. F. Beck, D. S. Chervinsky, Y.-C. Kim, D. M. Pitterle, and A. Hyland
Prognostic Significance of Molecular Genetic Aberrations on Chromosome Segment 11p15.5 in Non-Small-Cell Lung Cancer
J. Clin. Oncol., March 1, 2002; 20(5): 1353 - 1360.
[Abstract] [Full Text] [PDF]

 Clinical Cancer Research [► HOME](#)

P. P. Claudio, M. Caputi, and A. Giordano
The RB2/p130 Gene: The Latest Weapon in the War against Lung Cancer?
Clin. Cancer Res., March 1, 2000; 6(3): 754 - 764.
[Abstract] [Full Text]

 Cancer Research [► HOME](#)

L. Lin, S. Aggarwal, T. W. Glover, M. B. Orringer, S. Hanash, and D. G. Beer
A Minimal Critical Region of the 8p22-23 Amplicon in Esophageal Adenocarcinomas Defined Using Sequence Tagged Site-Amplification Mapping and Quantitative Polymerase Chain Reaction Includes the GATA-4 Gene
Cancer Res., March 1, 2000; 60(5): 1341 - 1347.
[Abstract] [Full Text]

 Carcinogenesis [► HOME](#)

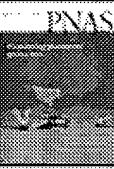
M. C. Stern¹, F. Benavides, E. A. Klingelberger, and C. J. Conti²
Allelotype analysis of chemically induced squamous cell carcinomas in F1 hybrids of two inbred mouse strains with different susceptibility to tumor progression
Carcinogenesis, July 1, 2000; 21(7): 1297 - 1301.
[Abstract] [Full Text]

 GENOME RESEARCH ► HOME

B. Gawin, A. Niederführ, N. Schumacher, H. Hummerich, P. F.R. Little, and M. Gessler
A 7.5 Mb Sequence-Ready PAC Contig and Gene Expression Map of Human Chromosome 11p13-p14.1
Genome Res., November 1, 1999; 9(11): 1074 - 1086.
[\[Abstract\]](#) [\[Full Text\]](#)

 CARCINOGENESIS ► HOME

T. Kohno and J. Yokota
How many tumor suppressor genes are involved in human lung carcinogenesis?
Carcinogenesis, August 1, 1999; 20(8): 1403 - 1410.
[\[Abstract\]](#) [\[Full Text\]](#)

 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES ► HOME

B.-W. Park, D. M. O'Rourke, Q. Wang, J. G. Davis, A. Post, X. Qian, and M. I. Greene
Induction of the Tat-binding protein 1 gene accompanies the disabling of oncogenic erbB receptor tyrosine kinases
PNAS, May 25, 1999; 96(11): 6434 - 6438.
[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

 THE AMERICAN JOURNAL OF PATHOLOGY ► HOME

J. H. Lichy, M. Zavar, M. M. Tsai, T. J. O'Leary, and J. K. Taubenberger
Loss of Heterozygosity on Chromosome 11p15 during Histological Progression in Microdissected Ductal Carcinoma of the Breast
Am. J. Pathol., July 1, 1998; 153(1): 271 - 278.
[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

 GENOME RESEARCH ► HOME

N. Kouprina, K. Kawamoto, J. C. Barrett, V. Larionov, and M. Koi
Rescue of Targeted Regions of Mammalian Chromosomes by in Vivo Recombination in Yeast
Genome Res., June 1, 1998; 8(6): 666 - 672.
[\[Abstract\]](#) [\[Full Text\]](#)

 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES ► HOME

C. Schwienbacher, S. Sabbioni, M. Campi, A. Veronese, G. Bernardi, A. Menegatti, I. Hatada, T. Mukai, H. Ohashi, G. Barbanti-Brodano, C. M. Croce, and M. Negrini
Transcriptional map of 170-kb region at chromosome 11p15.5: Identification and mutational analysis of the BWR1A gene reveals the presence of mutations in tumor samples
PNAS, March 31, 1998; 95(7): 3873 - 3878.
[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

[HOME](#) [HELP](#) [FEEDBACK](#) [SUBSCRIPTIONS](#) [ARCHIVE](#) [SEARCH](#) [TABLE OF CONTENTS](#)

Copyright © 1994 by the National Academy of Sciences